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13. ABSTRACT (Maximum 200 words)

The objective of the proposed work is to achieve efficient phase transfer catalysis in fluorophase. For this purpose, we had developed a new dendrimer design that can potentially be used as the amphiphilic nanocontainer. Since dendrimers are too expensive to synthesize, we are approaching novel polymers as the target nanocontainers to achieve the required properties. The dendrimer design however provides an avenue for the fundamental studies. In this report, we outline the design and synthesis of a new class of fluorocarbon based polymer micelles. The properties of these polymers are being investigated currently in our laboratories.

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Phase transfer catalysis is of interest in several aspects of organic reactions, since the reagents and substrates often have very different solubility properties. The U.S. Army has an interest in this area, since the chemical warfare agents are often hydrophobic and the corresponding anti-warfare agents are often hydrophilic. While a standard phase transfer catalyst such as tetraalkylammonium halides seem like an obvious choice, the process is more challenging due to the following reason. The current optimized procedure for removing warfare agents from surfaces of tanks, clothes, etc. involves fluorinated solvents. Although this treatment cleans the surface, the chemical warfare agent itself is not destroyed in the process. The chemical warfare agent is separately treated by passing the wash-solution through a filter bed. An attractive alternative is to be able to combine the wash and the destruction processes in one step. Thus, the challenge in such an approach is the following: the chemicals for the destruction process themselves involve two incompatible components, *viz*. the lipophilic warfare agent and the hydrophilic neutralizing reagent. The wash solution is fluorocarbon based, which is incompatible with both lipophilic and hydrophilic solvents. Therefore, there is a need for the ability to carry out a phase-transfer catalysis type reaction between a lipophilic substrate and a hydrophilic reagent in fluorinated solvents. Note that this phase-transfer catalysis is not typical, compared to what is commonly encountered in the literature. In the present case, the strategy should involve three phases. The classical phase-transfer catalysis reactions involve only two immiscible phases.

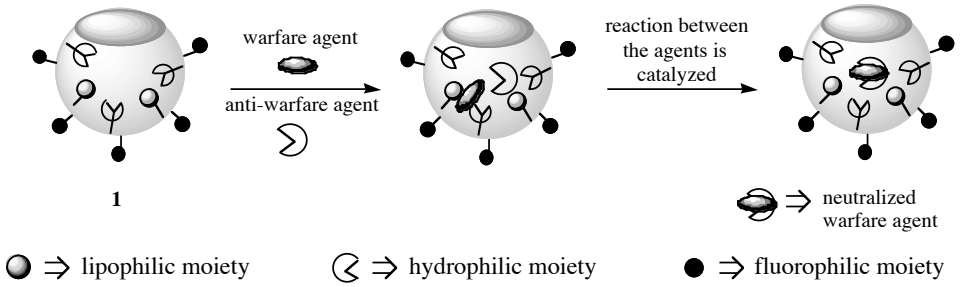


Figure 1. Representation of the Proposed Dendrimers for Phase Transfer Catalysis in HFE-3100

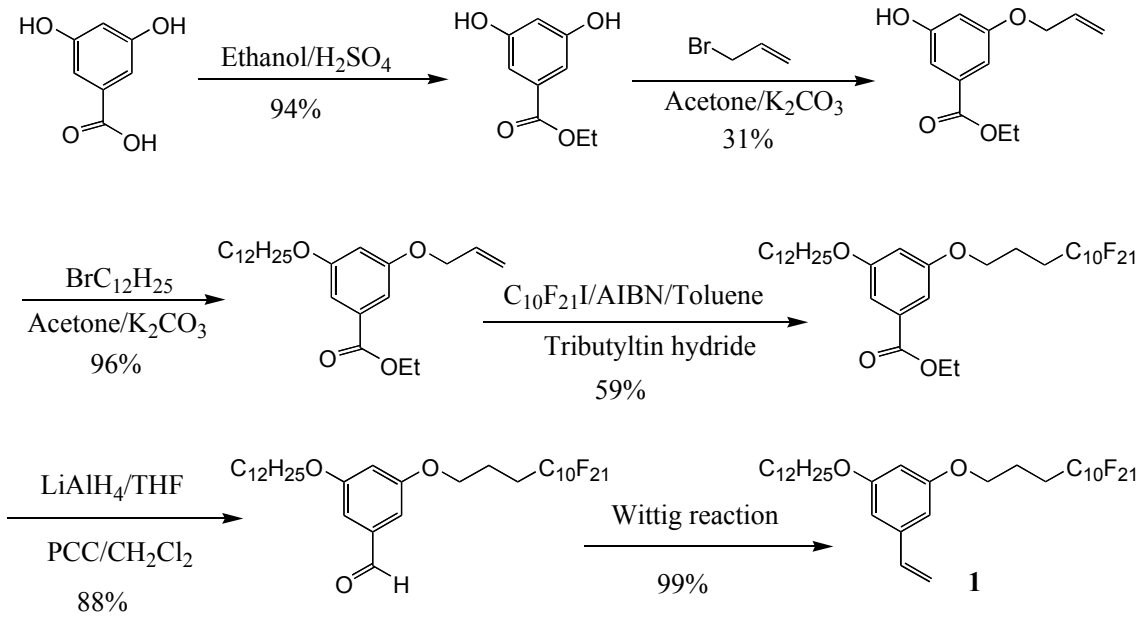
We proposed that facially amphiphilic macromolecules provide a unique opportunity to carry out such catalysis. In this case, the outer face of our macromolecules will contain fluorocarbon substituents, which will render the macromolecules soluble in solvents such as HFE-3100. The interior will be decorated with both hydrophilic and lipophilic substituents. This type of a supramolecular arrangement of substituents in the nanocontainers should render them capable of sequestering both hydrophilic and lipophilic substrates. A schematic representation of our approach is shown in Figure 1. We approached the design of macromolecules with both polymers and dendrimers.

Amphiphilic Polymers:

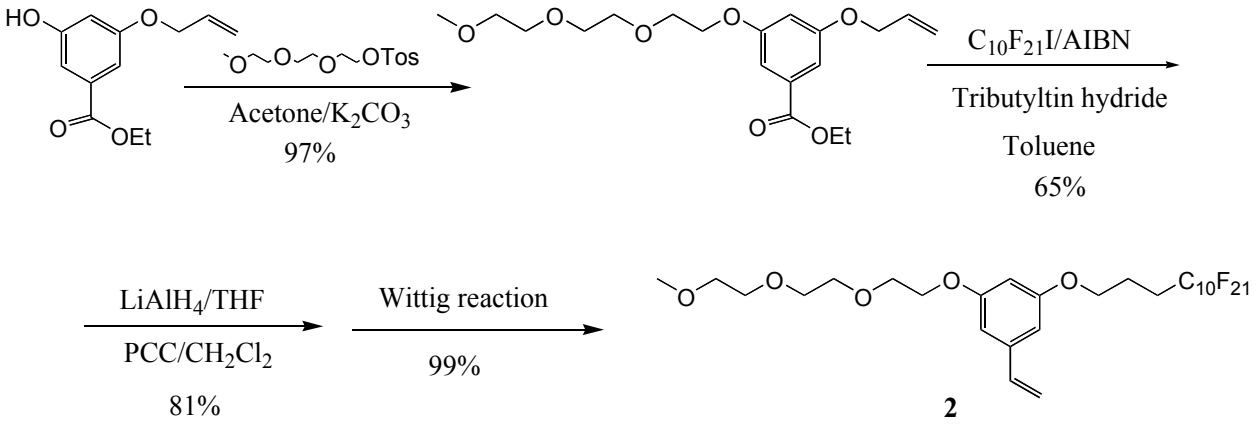
To achieve polymers containing fluorocarbon chains in one face and lipophilic and hydrophilic groups on the other face, we synthesized two styrene based monomers (**1** and **2**). The monomer **1** contains fluorocarbon and hydrocarbon chains, while the monomer **2** contains fluorocarbon and hydrophilic chains. The syntheses of the monomer started with commercially available 3,5-dihydroxybenzoic acid. At first, the ethyl ester of the benzoic acid was synthesized. Then, one of the two phenolic groups was converted to an allyloxy

moiety by alkylation under potassium carbonate conditions. Alkylation of the remaining phenolic group with dodecyl moiety proceeded smoothly. The allyl group was then used to attach a fluorocarbon chain under radical conditions to afford the ester that contains both fluorophilic and lipophilic chains. The benzoic ester moiety was then converted to an aldehyde followed by conversion to the substituted styrene monomer **1**. The synthetic strategy is shown in Scheme 1. Similar approach was taken to synthesize the monomer **2**, as shown in Scheme 2.

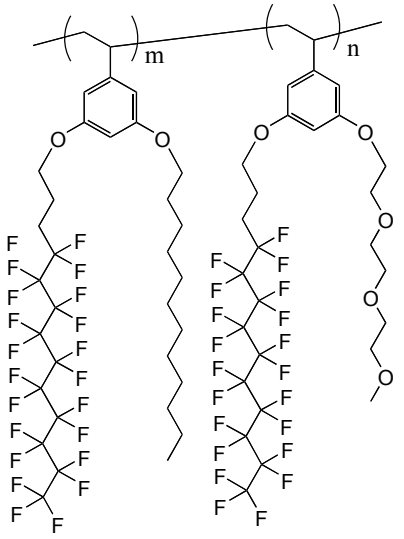
Scheme 1



Scheme 2



The random co-polymer **3** was achieved by radical polymerization using AIBN. The resultant polymer is soluble in the fluorocarbon solvent CFC-113, but is not soluble in FC-77. The solvent CFC-113 is also miscible with common organic solvents. Variations of this polymer are currently underway to increase the fluorocarbon solubility, including modification of the ratio of monomers **1** and **2**, as well as adjusting the length of the amphiphilic chains. Experiments are also underway to investigate whether microenvironments containing both lipophilic and hydrophilic moieties can be obtained in fluorocarbon solvents with these polymers.



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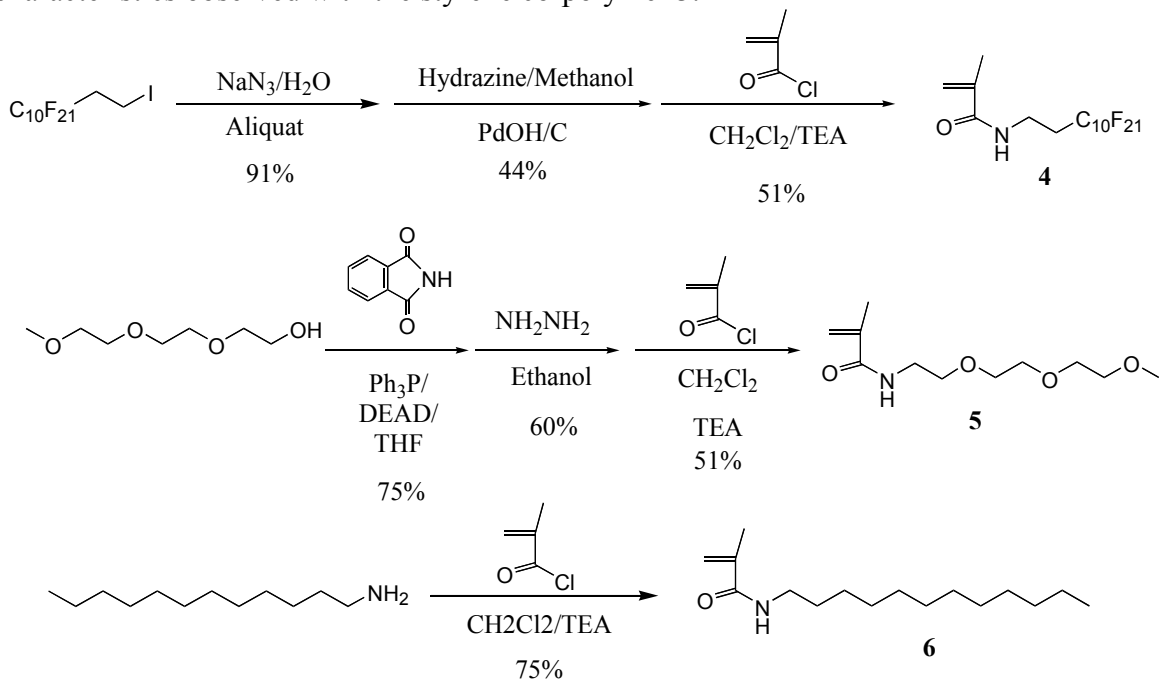
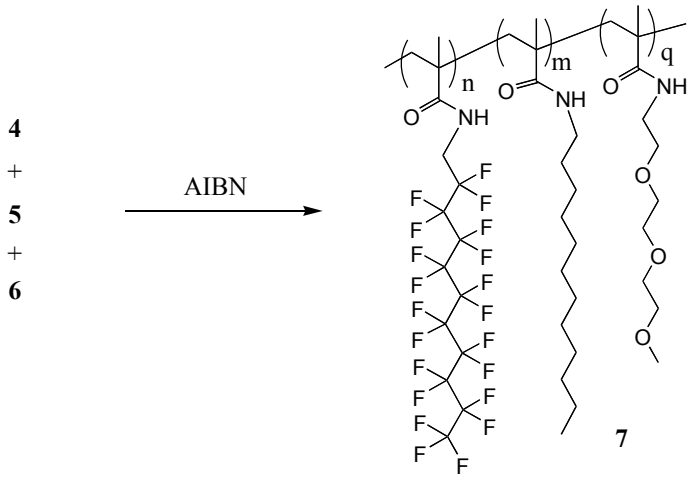
Similarly, we also synthesized polymers based on acrylamides. In this case, three different monomers containing hydrophilic, lipophilic, or fluorophilic functionalities were co-polymerized randomly in 1:1:2 ratio. Syntheses of the monomers and the corresponding polymer are shown below. The polymer **7** had similar solubility characteristics observed with the styrene co-polymer **3**.





Amphiphilic Dendrimers:

Our dendritic molecular design involves a monomer unit that places the AB_2 functional groups for the dendrimer growth and the amphiphilic functional groups in the planes perpendicular to each other. Therefore, when the monomer units are assembled to form dendrimers, the amphiphilic functionalities are either on the convex or the concave face of the dendrimer. A two-dimensional cartoon representation of the monomer structure and the dendrimer growth is shown in Figure 2. In this representation, the dendrimer growth is at the plane of the paper, and the amphiphilic moieties project in and out of the plane of the paper. When the dendrimer grows to be globular in shape from this atropisomeric monomer, the amphiphilic units would reside in a plane perpendicular to that of the dendrimer backbone. Thus, the convex and the concave faces of each monomer unit will be functionalized with groups of opposite polarity. Whether the fluorophobic or the fluorophilic group is at the convex face will be determined by solvophobic interactions.

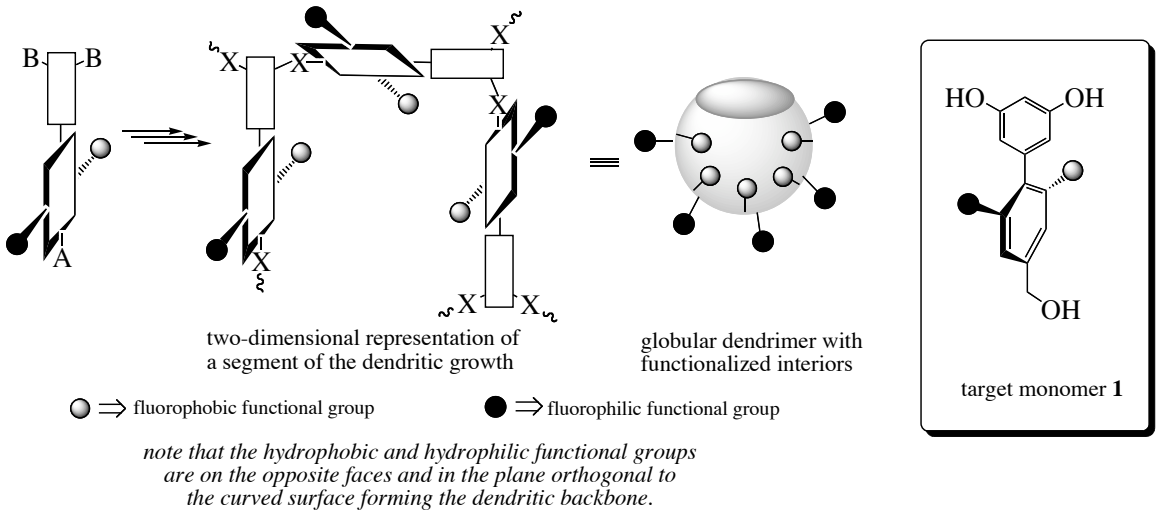


Figure 2. Representation of the AB_2 Monomer Unit and the Corresponding Dendrons with Amphiphilic Units in Orthogonal Planes

The first target structure is represented by the biphenyl molecule **8** (Figure 2). The AB_2 functionalities include the benzyl alcohol and the two phenolic moieties. The key feature of the design is the following: the two phenolic groups in one of the aryl rings are in the same plane as the benzyl alcohol moiety in the other aryl ring, since the benzyl alcohol substituent and the biphenyl linkage are *para*- to each other. Therefore, the relative geometry of the monomer functional groups in **8** is similar to that of the 3,5-dihydroxybenzyl alcohol, the classical monomer in benzylether dendrimer synthesis. However, the biaryl twist between the two aryl rings dictates that the fluorophobic substituent (hydrophilic and lipophilic substituents) and the fluorophilic moiety are in a plane perpendicular to that of the dihydroxybenzyl alcohol groups, as shown in the Figure 2. Since the fluorophilic and the fluorophobic groups are at the *ortho*- positions of the aryl ring, they will be placed at the

opposite faces of the dihydroxybenzyl alcohol plane. We do note that the atropisomeric twist is not necessarily 90°. A crude modeling study using Chem-3D shows the twist isabout 60°. This twist is sufficient to selectively functionalize the concave interiors of these globular dendrimers.

In order to utilize the dendrimers for the applications mentioned above, we have to perform systematic structure-property relationship studies in which the supramolecular disposition functional groups in these dendritic structures is identified. We have previously reported the synthesis of dendrimers based on the monomer **8** (*Org. Lett.* **2001**, *3*, 1961). In these dendrimers, the hydrophobic unit is a butyl moiety and the hydrophilic unit is a triethyleneglycolmonomethyl ether moiety. After the assembly of the dendrimer, we realized that these groups are not sufficient to render the dendrimers soluble in both polar and apolar solvents. In order to perform an effective structure-property relationship study with these dendrimers it is necessary that we are able to synthesize variations in hydrophilic, lipophilic, and fluorophilic units with significant synthetic efficiency. For this reason, we designed a monomer unit in which the substituents in the dendrimer would contain complementary protecting groups. After the assembly of the dendrimer, we should be able to remove one of the two protecting groups to install fluorocarbon functionalities. Following this transformation, we should be able to remove the second protecting group to install hydrophilic or lipophilic functionalities. The strategy is schematically outlined in Figure 3. This approach will lead to performing structure-property relationship studies with high efficiency. Our progress in the development of a synthetic strategy to perform such studies is outlined below.

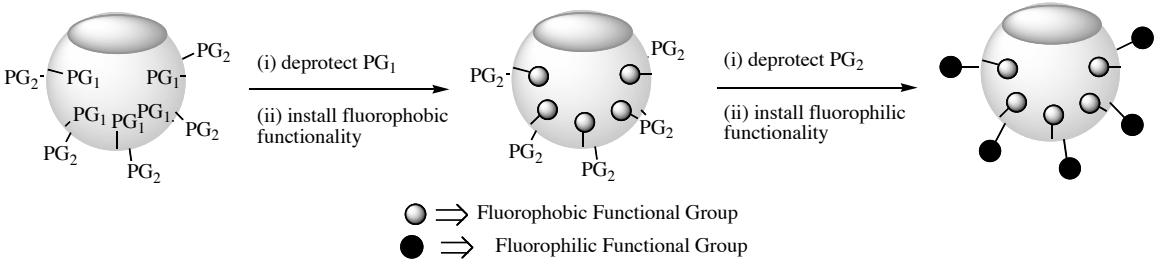
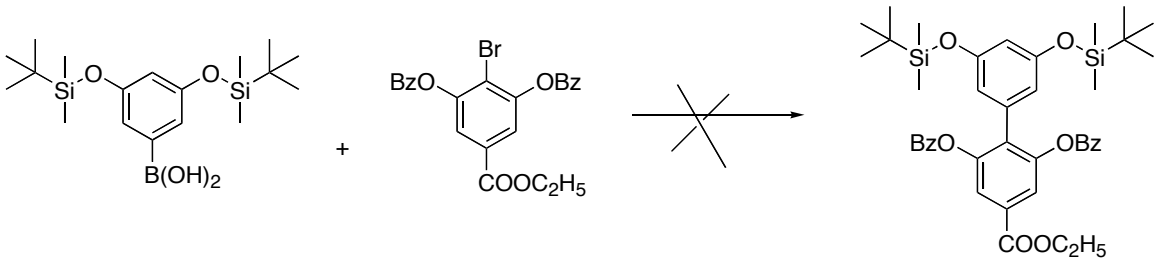
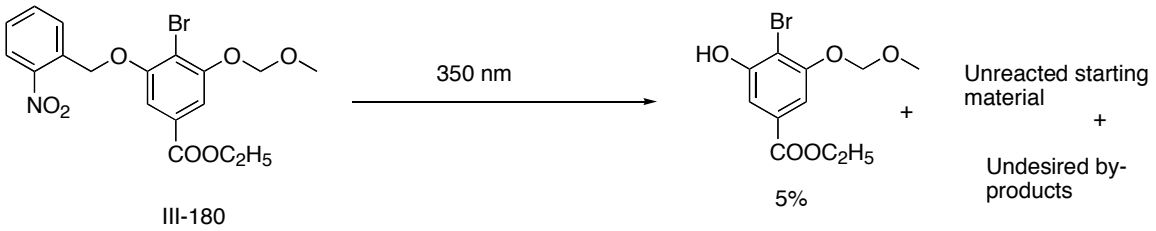


Figure 3. Representation of the Synthetic Strategy with Complementary Protecting Groups

The methoxymethyl ether (Mom) group was chosen as group **PG1**, since we had prior experience with carrying out the monomer synthesis with this protecting group. Various reactions were carried out to select a synthetically compatible and complementary protecting group **PG2**. We first attempted the Suzuki coupling to synthesize the desired monomer in the presence of various protecting groups, while also testing the compatibility of the deprotection procedure in the presence of the –Mom group. Accordingly, the following reaction was carried out; unfortunately no coupling product was isolated under the reaction condition.

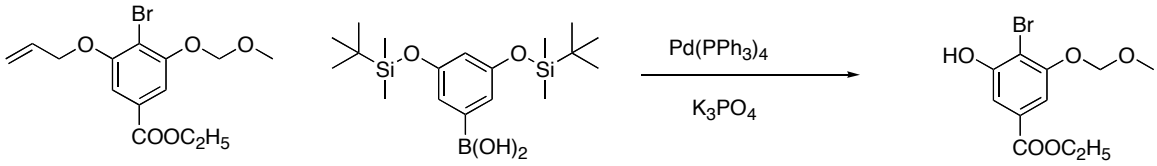


It has been reported that 2-nitrobenzyl group can be selectively cleaved under photochemical conditions. In order to test this possibility, the compound **III-180** was prepared and subjected to the photochemical reaction. Although 5% of the desired product was found by GC analysis, the remaining reaction mixture included a large amount of unreacted starting material and various side products. It is necessary that the deprotection reaction is very clean, since a large number of deprotection reactions are going to be carried out in a single molecule according to our strategy. Thus, an unclean reaction could result in complicated mixtures, when these deprotections are carried out with dendrimers.



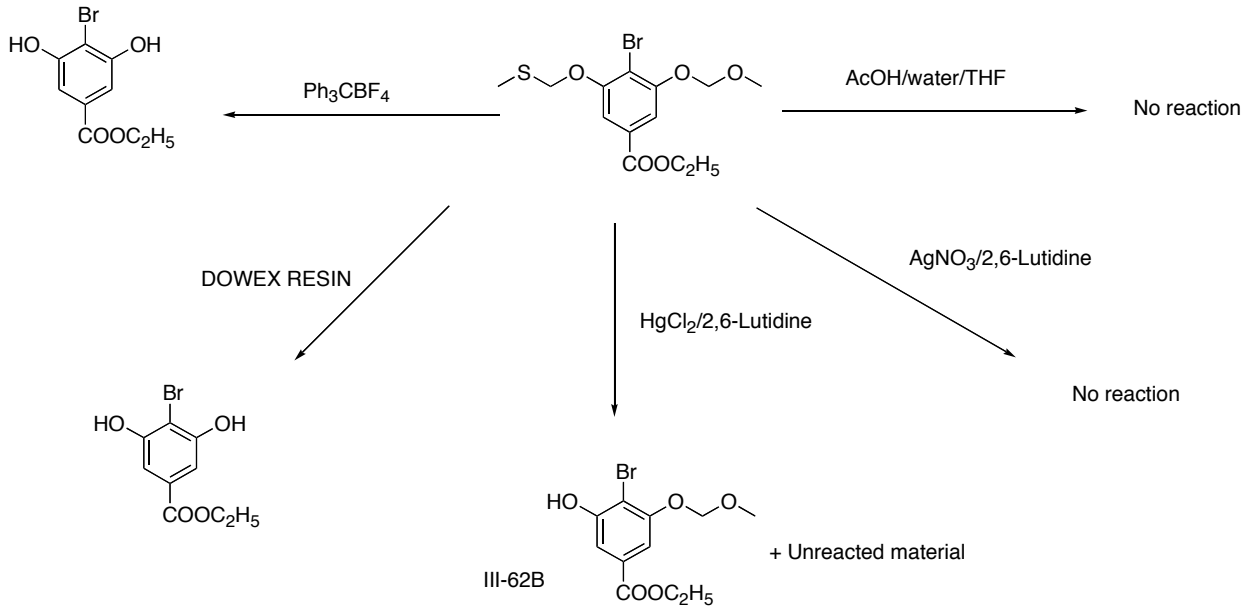
III-180

The allyl group is another versatile phenolic protecting group that has been used extensively in organic synthesis. When the compound **III-86** was used to get the biphenyl compound the allyl group was completely cleaved under the Suzuki reaction conditions. It is known that such deallylation can be effectively done using palladium catalyst in presence of reducing agent. We have utilized this observation to synthesize dendrimers with their periphery functionalized with diverse set of functional groups.



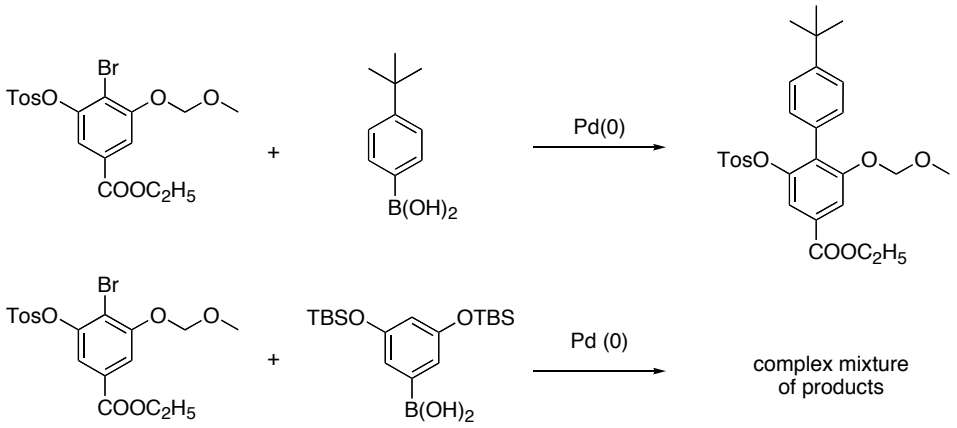
III-86

It has been reported that methylthiomethyl (MTM) ethers can be selectively cleaved in the presence of methoxymethylether (MOM) using heavy metal salts such as $HgCl_2$ or $AgNO_3$. The compound **III-104** was prepared and various reaction conditions were tried to achieve selective cleavage of MTM group. It was found that a mixture of acetic acid and water in THF did not either of the groups. The $HgCl_2$/2,6-lutidine system selectively cleaved the MTM group, but the deprotection could not be forced to completion. Dowex resin deprotects both functionalities unselectively. $AgNO_3$/2,6-lutidine did not produce any product; unreacted starting material was quantitatively recovered. No selectivity was observed also with trityl tetrafluoroborate as the reagent.

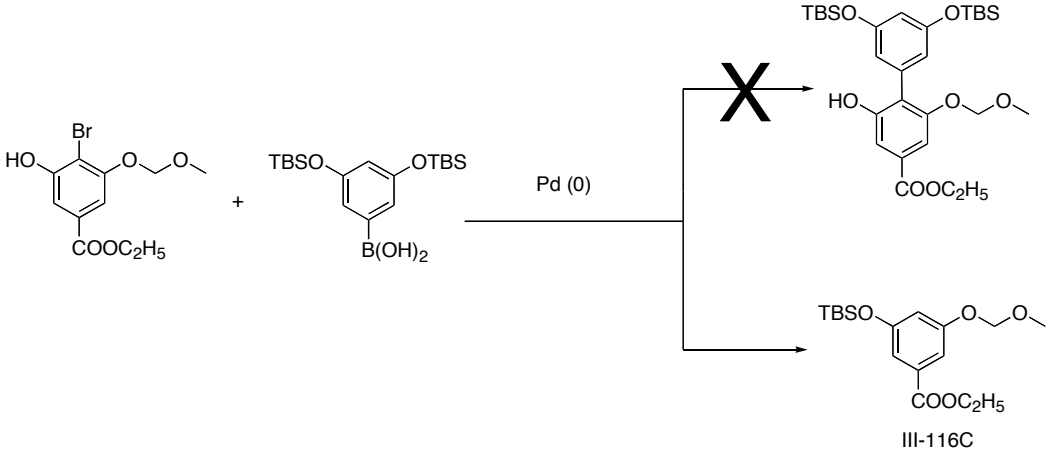


III-62B

Next, the possibility of using tosyl group as one of the protecting groups was examined. The bromoarene compound containing a tosyl group and a MOM group was prepared and a model reaction with 4-*tert*-butylphenyl boronic acid was studied. It was observed that the reaction goes well; but, when the same reaction was tried with TBS protected boronic acid, the reaction was unclean and we were unable to isolate the expected product.

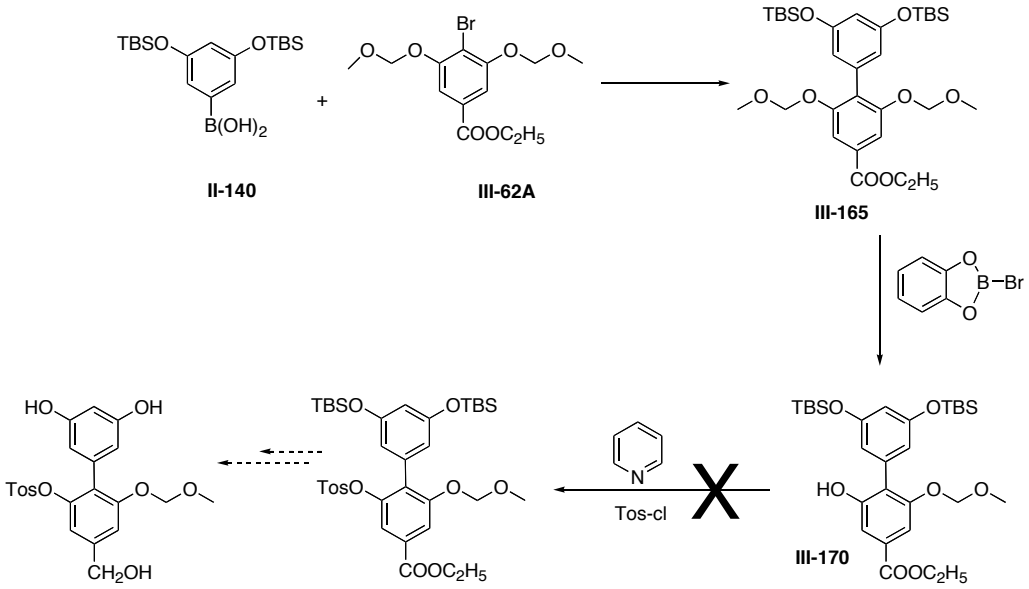


It is also known that Suzuki coupling can be carried out in presence of a free hydroxyl group. The following reaction was attempted to see if the expected biphenyl could be formed. Surprisingly, we noticed that the TBS- group migrated from the boronic acid compound to the bromoarene with concomitant debromination.



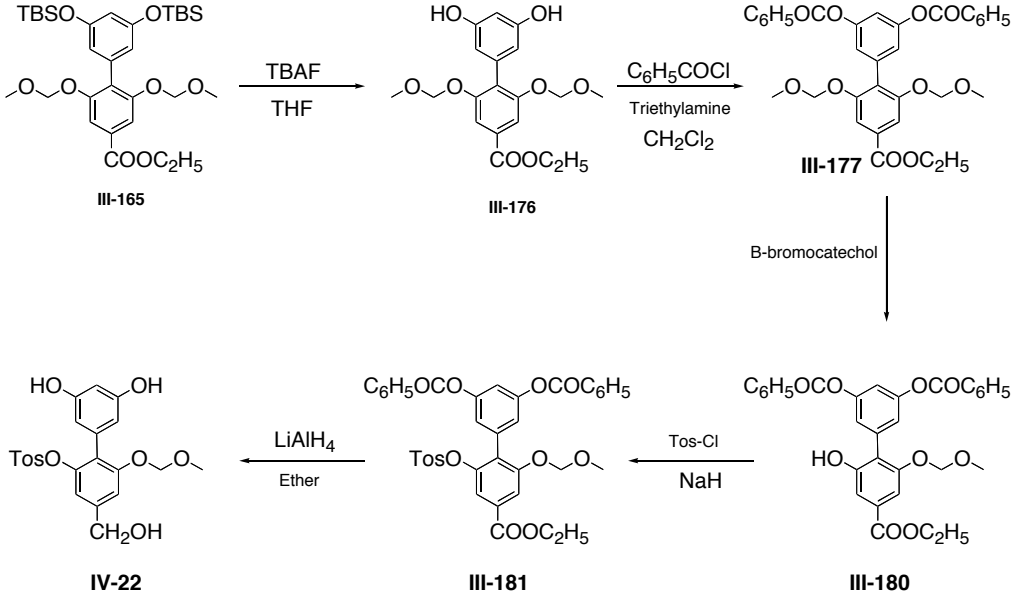
III-116C

In an alternate approach, we decided to install the group **PG2**, after the Suzuki coupling step. Accordingly, the compound **III-165**, which contains two –Mom protecting was prepared. Mono-deprotection of this compound was carried out using catecholboronbromide to afford the compound **III-170.** The attempted tosylation of this compound using pyridine as the base did not proceed. The use of sodium hydride or potassium carbonate as base is known to deprotect the TBDMS group and therefore could not be used.

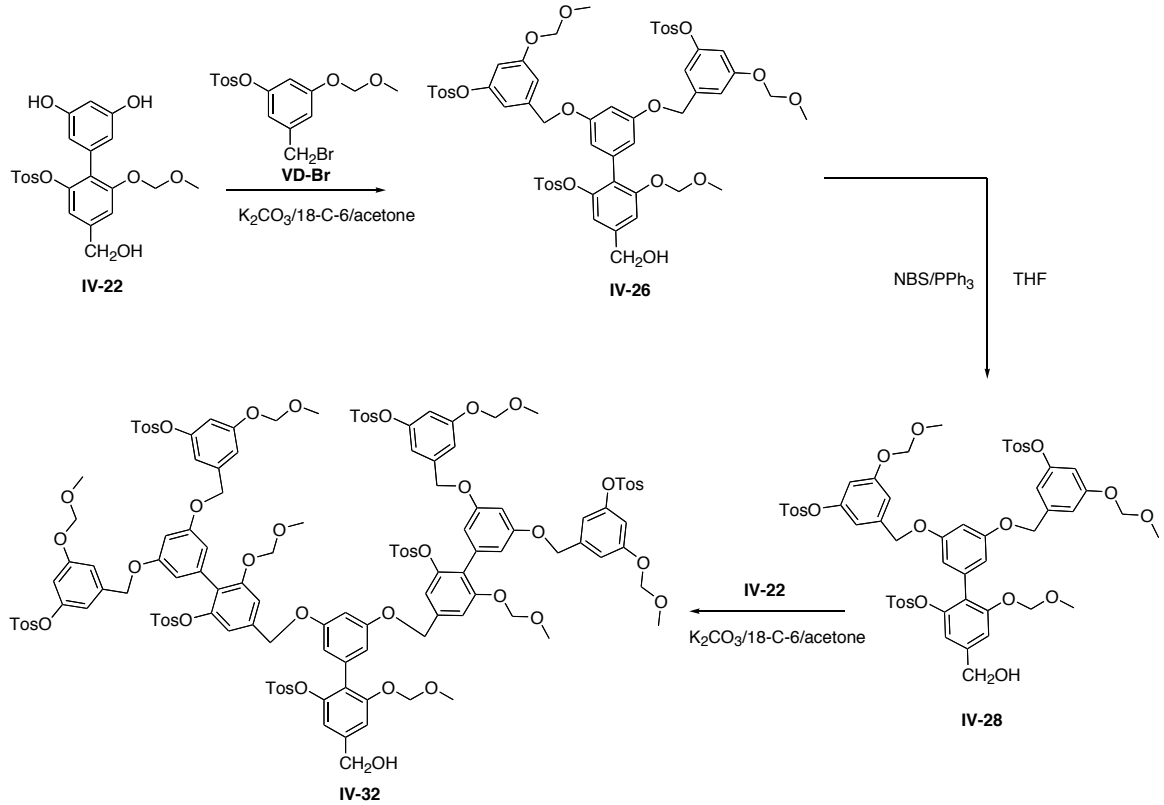


II-140 III-62A III-165 III-170

To overcome these problems, the synthesis of target monomer was pursued using a different approach as shown below. Here, the TBDMS groups were replaced with benzoyl groups in order to make the compound compatible to the reaction conditions involving tosylation with sodium hydride. This involved the deprotection of compound **II-165** to give **III-176,** which on benzoylation using benzoylchloride in presence of triethylamine gives the compound **III-177.** Using *B*-bromocatecholborane, the monodeprotected compound **III-180** was obtained. The benzoylation using NaH/Tos-Cl yielded the compound **III-181** which on $LiBH_4$ reduction gave the desired monomer **IV-22**.



Using the monomer **IV-22** as the repeat unit and **VD-Br** as the peripheral monomer, dendrons were assembled using the convergent synthetic protocols developed previously. In the Scheme below, we show the synthesis of a G2-dendron. Assembly of dendrimers from the dendrons **IV-28** and **IV-32** and the demonstration of quantitative protection and deprotection reactions are currently underway in our laboratories.



Summary:

In order to achieve phase transfer catalysis in a fluorocarbon solvent, polymers and dendrimers that should be capable of affording fluorophobic microenvironments have been synthesized. The expected unique feature of these macromolecules is that the interior would contain both lipophilic and hydrophilic functionalities. Our intention is to exploit this feature to perform phase transfer catalysis. The model reaction we will use for this purpose involves the hydrolysis of *p*-nitrophenyl esters, which can be easily monitored by UV-visible spectroscopic techniques. Efforts are underway in our laboratory to characterize the possible formation of these micelles and the ability of these micelles to act as nanocontainers for catalysis.

Publications and Presentations: Some of the synthetic results outlined here were reported in the American Chemical Society meeting in Orlando in April 2002 and New Orleans American Chemical Society Meeting in April 2003. More recent results were also discussed in the New York ACS meeting in Fall 2003.Both presentations were done in the organic or the polymer division of the ACS.

Scientific Personnel: Currently the funding supports a postdoctoral associate and partially funds another postdoctoral associate.